IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION

Sampling and Analytical Methods

No direct reading instruments are available for determining arsenic in the field. The dusts and fumes of inorganic arsenic compounds can be collected by standard filtration including tape sampler, electrostatic precipitation, or impingement methods.

Several procedures have been developed for analysis of arsenic in air. Dubois and Monkman [68] compared three widely used methods on samples from a variety of sources. The methods tested were Gutzeit, silver diethyldithiocarbamate, and iodine microtitration. They concluded that the silver diethyldithiocarbamate method was superior to the others, and recommended it because of its sensitivity, accuracy, and suitability over a wide range of concentrations. The American Conference of Governmental Industrial Hygienists evaluated this method [69] by comparing test results obtained by eight cooperating laboratories. It was found [69,70] sensitive enough to detect, in a 10 cu m air sample, 0.1 μg As/cu m or a maximum of 1.5 μg As/cu m. Thus, sampling times and flow rates must be adjusted to collect from 1.0 to 15.0 μg As in the sample. Arsenic is reduced to the trivalent state and converted to arsine in a Gutzeit generator. The arsine is passed through a scrubber into an absorber containing silver diethyldithiocarbamate in pyridine. The resulting red color is measured photometrically. [69,70]

Engineering Controls

Significant exposures are encountered both in the production of arsenic compounds and in their use, and good industrial hygiene practices must be followed to prevent adverse health effects. Where fumes may be present, as in the sintering and roasting of arsenic-bearing ores, complete enclosure and exhaust ventilation of the operation is essential. [71] Operations that agitate arsenic trioxide dust, eg grinding, screening, shoveling, sweeping, and transferring, require control since the dust is very fine and disperses easily. [5] When the operation has not been sufficiently enclosed and ventilated, supplemental protective clothing and respiratory protection may be needed until adequate engineering controls are installed.

Arsenic trichloride can cause irritation or ulceration on contact or may be absorbed through the skin with fatal results. [20,21] Since its vapor pressure at 25 C is sufficient to produce an air concentration of 14,000 ppm (104,000 mg/cu m), [71] its handling requires complete enclosure.

Agricultural uses of arsenic compounds may produce potentially hazardous exposures for nearby personnel. Engineering control methods used will depend on the equipment and techniques used to apply the chemicals. Protective clothing and respiratory protection may be needed as supplemental controls.

Biologic Evaluation

Arsenic absorbed into the human body is excreted in the urine, feces, skin, hair, and nails, and possibly a trace from the lungs. [3,5,6,26] Even at low doses, a proportion of absorbed arsenic is deposited in the skin, hair, and nails where it is firmly bound to keratin. [6] Storage in these metabolically "dead" tissues represents a slow route of elimination from the body.

Arsenic in hair has been used to monitor workers' exposure, [22,41] but the significance of arsenic in hair is obscured by the difficulty of distinguishing externally deposited arsenic from that systemically deposited in the hair. Camp and Gant [72] reported that "there is no way to differentiate 'interior' and 'exterior' arsenic." Similarly, Watrous and McCaughey [22] reported that once arsenic was deposited on the hair, it resisted washing with ether and water, and they considered determinations of arsenic in hair to be completely unreliable. The level of arsenic in fingernail and toenail parings reflects past absorption and is therefore useful forensically, but is less useful if the goal is to monitor current absorption.

Most authors agree that the urine is a major route of arsenic excretion. [3,6,24] Arsenic can be detected in the urine of people with no known exposure to arsenic, apparently derived from dietary and general environmental sources. [2,4] However, the urine of workers occupationally exposed to arsenic may show much higher levels than that of the unexposed, even in the absence of signs of systemic arsenic poisoning. [4,39,22]

Webster [23] collected urine samples from 26 adults and 17 children and reported that the average arsenic content was 0.014 mg As/liter with an average specific gravity of 1.017. Corrected to a specific gravity of 1.024, Webster's average was 0.02 mg As/liter.

Schrenk and Schreibeis [4] collected 756 urine specimens from 29 persons with no known industrial exposure to or abnormal dietary uptake of arsenic. The overall average urinary excretion was 0.08 mg As/liter, and 79% of the samples were less than 0.1 mg As/liter. After the authors found that seafood could affect urinary arsenic levels, they excluded values when it was known that the subject had eaten seafood. However, some values, which apparently had been influenced by seafood, were included before seafood was recognized as a factor. Since no record of diet had been kept, these unusually high values could not be excluded (the three highest samples were 2.0, 1.1, and 0.42 mg As/liter).

Seafood was considered [4] to be the main source of dietary arsenic. Shellfish in particular elevated the arsenic of test subjects. In one test, three subjects with pretest levels of 0.01, 0.03, and 0.05 mg As/liter were given lobster tail for lunch. Four hours after eating, urinary levels were 1.68, 0.78, and 1.40 mg As/liter, respectively. Ten hours after eating, levels were 1.02, 1.32, and 1.19 mg As/liter. After 24 hours values were 0.39, 0.39, and 0.44 mg As/liter, and at 48 hours, values were approaching the pretest levels.

Rapid initial excretion of inhaled arsenic was reported by Holland et al, [24] with 28% of the absorbed As-74 being excreted in the urine within the first day after it was inhaled, and 45% within 10 days. An

additional 2.5% had been excreted in the feces after 10 days, but the remaining 52.5% was not accounted for.

Pinto and McGill analyzed [39] the urine of 348 men (845 spot samples) occupationally exposed to arsenic trioxide and reported a mean level of 0.82 mg As/liter. The median value was 0.58 mg As/liter, and 27.3% of the samples exceeded 1.0 mg As/liter. One hundred forty-seven urine samples from 124 active smelter employees considered to have no arsenic exposure averaged 0.13 mg As/liter. The three highest values were 0.53, 0.70, and 2.06 mg As/liter, but 88% of the samples were below 0.2 mg As/liter. Although it was stated that among the exposed workers there was only one dubious case of mild systemic arsenic poisoning, there were several cases (at least 17) of acute arsenical dermatitis. Over a 6-day period, sixteen of these had average urine arsenic levels, during or following British Anti-Lewisite (BAL) therapy, ranging from 0.30 to 0.93 mg As/liter. One individual with severe facial dermatitis of rapid onset received BAL every six hours for four days, but excreted an average of only 0.2 mg As/liter. It was surmised that this man was hypersensitive or allergic to arsenic. One individual who declined BAL therapy had urinary arsenic levels ranging from 3.15 to 5.76 mg As/liter over a two-day period. According to these authors, [39] individuals may show urinary arsenic levels in spot samples as high as 4 or 5 mg As/liter, without any evidence of systemic arsenic poisoning.

In the English sheep-dip factory, [41] urinary arsenic levels were determined for workers exposed to mixed arsenic trioxide and sodium arsenite dusts, and for unexposed controls. The urinalyses of exposed

personnel were repeated after an interval of six months. The mean urinary arsenic level for 54 controls was 0.085 mg As/liter, and in 58 determinations made on chemical workers (the most heavily exposed group), the mean was 0.231 mg As/liter (computed from the data given in Tables 6 and 7 by Perry et al [41]). The 3 highest levels recorded in the exposed group were equivalent to 0.73, 1.01, and 1.91 mg As/liter. Most of the chemical workers (28 of 31) had evidence, in the form of pigmentation and warts, of past systemic arsenicalism. Air samples were collected at a number of locations where chemical workers apparently were employed, and the mean arsenic concentration in these areas can be computed from data in Table 3 [41] as 0.562 mg As/cu m.

Thus, urinary arsenic levels of people with no known arsenic exposure have been reported as 0.014 (0.020 corrected to a specific gravity of 1.024), [23] 0.08, [4] 0.085, [41] 0.129, [22] and 0.13 mg As/liter. [39] Some of the unexposed individuals tested had urinary levels as high as 2.0 mg As/liter, [4,39] but these high levels may have been due to unusual dietary intake [4] or to unrecognized arsenic exposure. [39]

The urinary arsenic levels of exposed workers vary widely and levels above 4.0 mg As/liter have been reported [39] without apparent adverse effects. On the other hand, signs of mild systemic poisoning have been reported [22] in a worker excreting only 0.76 mg As/liter. This wide variability in urinary arsenic levels, even in an apparently unexposed population, combined with inability to demonstrate a definite association between urinary levels and either observed effects or atmospheric concentrations makes interpretation of urinary data difficult.

Nevertheless, a biological threshold limit value of 1.0 mg As/liter of urine was proposed by Elkins. [73] This was considered to be roughly consistent with a time-weighted average air level of 0.5 mg As/cu m. [74]

Of all the papers discussed in this document, only Webster [23] reported the specific gravity of the sample tested. Elkins, [73,74] Elkins and Pagnotto, [75] Buchwald, [76] and Levine and Fahy [77] all point out the importance of correcting to a mean specific gravity in order to obtain meaningful and consistent results. Testing persons in the United Kingdom, Buchwald [76] reported the mean specific gravity was 1.016. However, in the United States, Elkins, [73,74] and Elkins and Pagnotto [75] recommend 1.024. This was based on the findings of Levine and Fahy, [77] who in 1945 reported 1.024 as the mean specific gravity of nearly 1,200 urine samples. According to Elkins and Pagnotto, [75] their laboratory has analyzed 1,000 to 2,000 urine samples annually since the Levine and Fahy report, and 1.024 is still the mean specific gravity used. However, care must be exercised when making specific gravity corrections to express the specific gravity of the urine in relation to that of water at the same temperature. If a urinometer calibrated against water at 4 C is used, then a correction for temperature should also be employed. [75,77]

Citing urinary levels reported by Pinto and McGill [39] for exposed workers with no signs of poisoning, Schrenk and Schreibeis [4] concluded that, while no relationship could be shown between urinary arsenic levels and evidence of poisoning, "urinary arsenic levels in a group of exposed persons may serve to check the efficacy of control measures and indicate if excessive absorption of arsenic occurs." Referring to the inconsistency

with which the workers wore their respirators, Pinto and Bennett [48] wrote: "It is for this reason we depend on the urinary arsenic level as showing the men are exposed to arsenic-containing dusts. The simple measurement of arsenic dust in the air is not a good measure of how much arsenic has been absorbed by an individual."

Monitoring urinary arsenic cannot replace monitoring atmospheric concentrations as the primary method of characterizing the workers' exposure. It seems reasonable that group averages may be useful as a check on the adequacy of the overall program of engineering controls and work practices designed to protect the workers' health.

V. DEVELOPMENT OF THE STANDARD

Basis for Previous Standards

The American Standards Association (now the American National Standards Institute) in 1943 proposed 0.015 mg As/cu m as an American War Standard for inorganic arsenic. [78] However, the summary of standards compiled by Cook [79] shows that by 1945 the War Standard had been increased by a factor of 10 to 0.15 mg As/cu m, set on the basis of analogy with other metals such as cadmium and lead. The 0.15 mg As/cu m standard was also adopted by Connecticut, Massachusetts, New York, and Oregon, but Utah endorsed a Maximum Acceptable Concentration (MAC) of 0.5 mg/cu m. [79] In his discussion of the 0.15 mg As/cu m standard, Cook stated that "On the basis of long experience [undescribed] involving many occupational exposures, at least one large concern considers it permissible to increase the limit to 5. mg. per cubic meter."

In 1947 the American Conference of Governmental Industrial Hygienists (ACGIH) adopted an MAC for arsenic of 0.1 mg/cu m, [80] but the following year this was raised to a Threshold Limit Value (TLV) of 0.5 mg As/cu m. [81] The ACGIH gave no explanation for the change, but Pinto, commenting in a July 1972 written communication to ANSI on the 0.5 mg As/cu m standard, stated that arsenic trioxide was considered to be the primary arsenic compound to which there was industrial exposure, and the 0.5 mg As/cu m level was suggested as a safe concentration of arsenic trioxide, with "safe concentration" meaning that "it would not cause incapacitating dermatitis in a few hours." Whether the change from an MAC to a TLV constituted a change from a ceiling of 0.1 mg/cu m to a time-weighted

average of 0.5 mg/cu m is not clear. If that was the case and one applies the excursion factor of 3 presently recommended by the ACGIH [82] for TLVs in the 0.0 to 1.0 mg/cu m range, this change constituted a 15-fold increase. The present TLV recommended by the ACGIH is 0.5 mg As/cu m for "arsenic and compounds." [82]

In his 1959 textbook, Elkins [73] recommended a maximum allowable concentration of 0.25 mg/cu m for arsenic trioxide, equivalent to 0.19 mg As/cu m. There was little discussion given of safe exposure levels, but the Watrous and McCaughey [22] report of concentrations averaging almost 0.2 mg As2O3/cu m in the manufacturing department of a pharmaceutical plant apparently was a major consideration.

Separate TLVs for lead arsenate and calcium arsenate have been recommended by the ACGIH for a number of years. A limit of 0.15 mg/cu m for lead arsenate (equivalent to 0.026 mg As/cu m) was adopted tentatively in 1956, [83] confirmed in 1957, [84] and has remained unchanged since. [82] According to the ACGIH Documentation, [85] this compound was considered to present the double hazard of both lead and arsenic intoxication. The chronic toxicity was attributed to the lead content and the acute toxicity to the arsenic, although it was considered less acutely toxic than calcium arsenate. [85]

A limit of 0.1 mg/cu m (equivalent to 0.038 mg As/cu m) for calcium arsenate was originally recommended by the ACGIH in 1956, [83] and was adopted in 1957. [84] In his review of standards, Smyth [86] attributed the toxicity of calcium arsenate to the arsenic content. Considering it to be 20% arsenic, he recommended a standard of 2.5 mg/cu m to be consistent

with the ACGIH recommended standard of 0.5 mg As/cu m for "arsenic and compounds." The ACGIH documentation [85] cited Smyth [86] as attributing the toxicity to the arsenic content, but the TLV recommended for calcium arsenate was 1.0 mg/cu m (equivalent to 0.38 mg As/cu m). This discrepancy was not explained.

The Czechoslovak MAC Committee suggested a "mean MAC" of 0.3 and a "peak MAC" of 0.5 mg As/cu m. [87] The documentation did not give reasons for the levels chosen, but did state the following MACs for other countries: Great Britain, the United States, West Germany, and Yugoslavia, 0.5 mg As/cu m; East Germany, Hungary, and the USSR, 0.3 mg As/cu m; and Poland, 0.15 mg As/cu m. It was not stated whether these MACs were ceilings or time-weighted averages.

The present Federal standard for "arsenic and compounds" is 0.5 mg As/cu m as a time-weighted average. There are separate standards, both determined as a time-weighted average, for calcium arsenate (1.0 mg Ca3(AsO4)2/cu m) and for lead arsenate (0.15 mg Pb3(AsO4)2/cu m). [29 CFR 1910.93, published in the Federal Register, vol 37, dated October 18, 1972] These standards were based on the ACGIH recommendations.

Basis for Recommended Environmental Standard

A number of signs and symptoms are associated with arsenic poisoning. When ingested, arsenic compounds can cause nausea, vomiting, and diarrhea within a few hours, [25,27] although in at least one animal study [50] with arsenic trioxide, much of the gastrointestinal irritation was attributed to impurities. Dermatitis may be observed [25] after

chronic ingestion, but the typical signs of chronic arsenicalism are hyperpigmentation and hyperkeratosis, especially on the palmar and plantar surfaces, [25,27,33] and peripheral neuropathy [25,27] in a glove and stocking distribution with prickly sensations [25,29] and loss of distal proprioception and deep tendon reflexes. [25] Changes in the ECG have been reported after both acute [31,32] and chronic [29,32] intoxication, although in at least one report [25] of severe chronic arsenicalism, the patient's ECG was normal. ECG changes that were observed [29,31,32] regressed after arsenic exposure ceased. Anemia and leucopenia were reported [27] in cases of chronic intoxication, but these changes also regressed after arsenic ingestion ended. Effects on the liver include cirrhosis after prolonged use of Fowler's solution, [33] and, in animal studies, marked enlargement of the bile duct [55] and fatty degeneration of the liver. [57] Skin cancer has long been considered [10] a consequence of arsenic exposure, but multiple cancers of the viscera have also been reported. [36] However, the association too often was made because a cancer patient exhibited hyperpigmentation and hyperkeratoses. On this basis, cases were included both in Neubauer's review [10] in which 147 cases were collected and in the cases reported by Sommers and McManus [36] despite the fact that in some cases there was no known arsenic exposure.

No reports were found of occupational exposure to arsenic compounds resulting in nausea, vomiting, diarrhea, or peripheral neuropathy. Occupational exposures have been reported to cause hyperpigmentation, [28,41] palmar and plantar hyperkeratoses, [28] warts, [28] contact dermatitis and sensitization, [37-39] ulceration and perforation of the nasal septum,

[38,39] and conjunctivitis. [39] Reversible ECG changes [30] and severely reduced peripheral circulation resulting in gangrene of the fingers and toes [28] have been reported. Cirrhosis of the liver has been observed, [28,46] and one epidemiological study [49] reported significantly increased mortality due both to cirrhosis of the liver and to cardiovascular disease. Two studies reported that cancer [42,48] and cardiovascular [48] mortality were not significantly increased in workers exposed to arsenic, but the mortality experience of workers in the same plant studied by one of these [48] was examined again [47] in 1973 and significantly increased lung cancer mortality was reported. Other studies have reported cancer of the skin, [40,46] lung, [40,46,49] and other organs. [46] In general, attempts to produce cancer experimentally in animals have failed, [55,56,65,66] but leukemia reportedly [67] has been induced experimentally and teratogenic effects have been observed in animals. [60-62]

Atmospheric data were not included in the studies reporting dermatitis, [37-39] ulceration and perforation of the nasal septum, [38,39] conjunctivitis, [39] ECG changes, [30] disturbed peripheral circulation, [28] or cirrhosis of the liver. [28,46] The question of air levels was approached only by Pinto and McGill, [39] who considered dust-in-air measurements to be of limited value for predicting skin reactions.

ECG changes reported after nonoccupational [29,31,32] and occupational [30] exposure to arsenic have apparently been reversible. One epidemiological study [48] of a copper smelter reported that observed deaths due to cardiovascular disease exceeded the expected, but the difference was not statistically significant. Another study [49] of a smelter population

found that, compared to statistics for the state in which the smelter was located, mortality due to heart disease was significantly increased. In terms of length of employment, cardiovascular mortality was significantly increased in 4 of 5 cohorts, and the excess mortality was approximately the same in each of these 4 cohorts. In both smelter studies, [48,49] exposures were to many compounds other than arsenic. However, the fact remains that arsenic apparently caused at least temporary ECG changes [29-32] and may have caused increased cardiovascular mortality. [48,49]

Cirrhosis of the liver has been reported as a result of prolonged use of Fowler's solution [33] and among German vineyard workers. [28,46] In the latter studies, ethyl alcohol may have been at least a contributor, since in one report [28] many of the vineyard workers were said to drink 2 liters or more of wine daily. A recent epidemiological study [49] of an American smelter population found increased mortality due to cirrhosis of the liver, but the increase apparently was not related to length of exposure. Animal studies have reported liver damage after ingestion of either sodium arsenite or arsenate [55] and after inhalation of arsenic trioxide. [57] Thus the potential for liver damage seems real, but it is not clear whether occupational exposures have actually resulted in damage, and if so, at what concentration.

Two mortality studies [42,48] of smelter populations have reported that observed cancer mortality exceeded the expected mortality but not significantly. These authors concluded that workers exposed to arsenic did not experience increased cancer mortality, but that conclusion is open to question. In the Snegireff and Lombard study, [42] the authors examined

and discussed only overall cancer mortality. However, according to a comparison made by NIOSH, respiratory cancer mortality as a proportion of total cancer deaths was 5.7 times expected in the plant at which arsenic trioxide was handled and 6.5 times expected in the comparison plant at which arsenic was not handled. Thus, both plants apparently had increased respiratory cancer mortality, although overall cancer mortality was not significantly increased.

The Pinto and Bennett study [48] was followed in 1973 by the Milham and Strong report [47] of mortality among workers at the same plant. These authors [47] found that lung cancer mortality was significantly higher than expected. As reported by Hill and Faning, [40] the cancer mortality of chemical workers in the English sheep-dip factory was significantly increased. The small numbers involved made firm conclusions difficult, but the authors suggested that the excess could be attributed to increased lung and skin cancer mortality. Lee and Fraumeni [49] reported not only that respiratory cancer mortality was significantly increased, but also that the incidence of respiratory cancer increased with length of employment as well as with the degree of arsenic exposure.

These studies [40,47,49] strongly implicate arsenic as an occupational carcinogen. However, the relationship is obscured because, in the smelting industry, the workers were exposed to a variety of substances other than arsenic, one of which was sulfur dioxide. In the Lee and Fraumeni report, [49] lung cancer mortality increased with increasing arsenic exposure; but generally the sulfur dioxide levels increased with the arsenic levels. It was not possible to examine the mortality of a

arsenic exposure; but generally the sulfur dioxide levels increased

subgroup exposed only to arsenic or only to sulfur dioxide, so a role by sulfur dioxide or some other substance cannot be ruled out in the smelting industry. However, the involvement of arsenic can hardly be denied. There was no suggestion of sulfur dioxide exposure in the sheep-dip factory, [40,41] but cancer mortality was still significantly increased. [40]

Environmental data with which to establish a safe exposure level are scant. In the English sheep-dip factory study, [40,41] increased cancer mortality was observed among chemical workers. [40] The average exposure of chemical workers can be computed as 0.562 mg As/cu m from the air concentrations reported by Perry et al [41] by assuming that all samples reported, with the exception of 6 samples from the packing room where workers apparently would be classified as packers, were collected in areas in which chemical workers were employed. Increased lung cancer mortality was reported by Lee and Fraumeni [49] in all cohorts, including the group with only 1 to 4 years of employment, and in all exposure groups, including those with light arsenic exposure. The sparse data (12 samples from three "light" exposure areas) with which to characterize these work areas range from 0.001 to 1.20 mg As/cu m with a mean and median of 0.206 and 0.01 mg As/cu m, respectively (Table XI-3). With the exception of the pharmaceutical plant study, [22] no environmental data were published in any of the other reports examined.

Even if contact dermatitis and systemic toxicity were the only bases for establishing a standard, it is evident that the existing Federal standard of 0.5 mg As/cu m is too high because, according to Pinto in a July 1972 written communication to ANSI, it was originally established to

standard of 0.5 mg As/cu m established

prevent "incapacitating dermatitis in a few hours," clearly an inadequate basis from present-day considerations. However, more recent reports [40,47,49] associate inorganic arsenic with occupational cancer. The Lee and Fraumeni report [49] strongly suggests that exposure at or around 0.2 mg As/cu m [Table XI-3] can result in an increased incidence of cancer. Because of the seriousness of the disease, prudence dictates that the standard should be set at least as low as 0.05 mg As/cu m. It is believed that exposure at this level should, at the minimum, significantly reduce the incidence of arsenic-induced cancer.

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